any information essential to the invention disclosed and claimed in the application. Canceling this figure from the application renders moot the objections to the figure set forth in PTO Form 948. Formal drawings with the corrections as discussed above will be submitted to the Patent Office upon an indication of allowable subject matter by the Examiner.

The remaining amendments to the specification set forth above are made to correct obvious typographical and grammatical errors in the specification as originally filed. No new matter is presented by any of these amendments.

In addition, claims 15-27 and 31 have been canceled from the application. Applicants reserve the right to file a continuation application directed to the subject matter of these claims.

The examiner has rejected all of the claims pending in this application under 35 U.S.C. § 101 on the basis that the invention as disclosed is inoperative and, therefore, lacking utility. The examiner stated that no evidence is presented in the application to support the allegation in the specification that the antibodies of the invention are useful in therapeutic regimens. The examiner asserted that pharmaceutical therapies in the absence of *in vivo* clinical data are unpredictable for several reasons: the protein can be inactivated before producing an effect, the protein may not reach the target area and other functional properties "known and unknown," such as adverse side effects, could make the protein unsuitable for *in vivo* therapeutic use.

As an initial point, it should be noted that the examiner has not provided any support for his assertion that these three "reasons" are applicable to the invention of the application. His stated reasons are mere assertions that are not supported by a single cited reference. The examiner provides no citations demonstrating that any particular protein, used as a therapeutic, is inactivated by proteolytic degradation or immunological inactivation or is unable to reach its target because it is adsorbed by fluids, cells and tissues. With regard to his third statement, that functional properties "known or unknown" may make the protein unsuitable for *in vivo* use, Applicants wish to point out that Section 608.01(p) of the M.P.E.P. provides that "[i]f the asserted utility of a compound is believable on its face to persons skilled in the art in view of the contemporary knowledge in the art, then *the burden is on the examiner to give adequate support for the rejections for lack of utility under this section*", citing *In re Gazave* 154 USPQ 92 (CCPA) 1967). The examiner's unsupported statement that functional properties "known or unknown may make the protein unsuitable for *in vivo* use" does not meet the burden of the Patent Office and therefore is insufficient to form the basis for a rejection.

In making the rejection under § 101, the examiner cited *Brenner v. Manson*, 383 U.S. 519, 148 U.S.P.Q. 689 (1966). Applicants respectfully submit that the *Brenner* case is inapposite to the present situation. In *Brenner*, the applicants had disclosed a process for synthesizing a chemical compound

which had no known use. Applicants submitted only that the potential usefulness of the compound was under investigation by researchers and that a homolog of the compound had been found to have tumor-inhibiting effects in mice. In contrast to this, in the present application the applicants have stated not just that the primate antibodies have usefulness as "a therapeutic" but that they are useful for treating a number of specific, listed disorders. Absent evidence that the applicants' statements are untrue, their truthfulness must be accepted. See *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971).

Applicants further wish to point out that claims 1-14, the only claims now pending in the application, are directed to methods of producing recombinant antibodies or to vectors and cell lines useful in producing such antibodies. The specification notes that the recombinant antibodies produced in accordance with the method of this invention are useful in diagnostic methods as well as therapeutically (see page 19 of the specification). The examiner's concerns about the utility of the antibodies produced by the method of this invention seem to revolve around their usefulness as therapeutic agents. Although the Applicants disagree with the examiner's concerns regarding the utility of these antibodies as therapeutic agents, they also wish to point out that it is an accepted tenet of patent law that an invention meets the utility requirement of § 101 of the patent statute if it can perform *some* useful function for society. Utility as a diagnostic agent certainly comes within the meaning

of this term, and diagnostic tests utilizing antibodies are well known to persons of ordinary skill in the art. As the examiner has provided no evidence to dispute that the recombinant antibodies of this invention are useful as diagnostic agents, Applicants respectfully submit that he must accept as true the Applicants' statement regarding the utility of their recombinant antibodies as diagnostic agents, and *in vivo* therapeutic data need not be provided to meet the requirements of § 101 of the patent statute.

The specification has been objected to, and claims 1-27 and 31 rejected, under 35 U.S.C. § 112, first paragraph, on the basis that the application does not provide an adequate written description of the invention. The examiner asserted that the Applicants had not sufficiently disclosed how to use the recombinant antibodies as therapeutic agents for the treatment of humans. To the extent that this rejection has not been rendered moot by the cancellation of the method of treatment claims, the rejection respectfully is traversed.

Applicants respectfully direct the examiner's attention to page 20 of the specification, where the Applicants provide specific guidelines regarding dosages, treatment regimens and suitable carriers for the antibodies and routes of administration. Although one skilled in the art may have to carry out some experiments to determine the optimum dosage regimen for a particular patient, Applicants respectfully submit

that the general guidelines present in the application are such that any such experimentation would be merely routine.

Claims 1-2, 4-5, 7-10, 12-16 and 26-27 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Gillies et al. The examiner asserted that this reference teaches methods for the production of human antibodies from cDNA libraries. As noted above, claims 15-16 and 26-27 have been canceled. This rejection as it is applied to claims 1-2, 4-5, 7-10 and 12-14 is traversed.

The present invention is directed to a method of obtaining recombinant primate (human and non-human) antibodies. The method comprises obtaining lymphocytes capable of expressing a desired antibody and, if desired, stabilizing the lymphocytes through viral transformation and/or fusion to myeloma cells. Total cell RNA is isolated, then mRNA encoding the antibody is isolated from the total RNA. cDNA is synthesized and then inserted into a cloning vector. A host cell is transformed to get a cDNA library, which then is screened for cDNA encoding the constant and variable regions of the heavy and light chains of the desired antibody. The cloned cDNA encoding the heavy and light chains of the antibody is inserted into an expression vector under the control of expression signals. A host cell is transfected with the expression vector and then cultured under antibody-producing conditions and the antibody so produced is isolated.

Gillies et al. also disclose a method for the production of primate antibodies. Unlike Gillies et al., however, the present Applicants teach inserting cDNA encoding the *entire* heavy and

light chains into an expression vector for transfection into the host cell. The method of the present invention encompasses inserting both the complete variable and constant regions of each of the heavy and light chains into the expression vector. In contrast to this, the cDNAs encoding the heavy and light chains spliced into a vector by Gillies et al. provided only *part* of the constant regions of the antibody (see figure 2 of the Gillies et al. paper). Gillies et al. teach that the variable regions of the antibodies are obtained solely from cDNA but that part of the constant region is supplied by genomic DNA of the same Ig subclass. From their comments, it is apparent that Gillies et al. believed that the entire cDNA of the antibody was not stable and that genomic DNA needed to be provided for the antibody being produced to function.

This use of a combination of genomic DNA and cDNA clearly is different from the teachings of the present invention in which cDNA encoding both the variable and constant regions of each of the light and heavy chains of the desired antibody have been used in the construction of the expression vectors used for the production of the desired antibody. Applicants' method is advantageous in comparison to the method taught by Gillies et al; Applicants' method is simpler and does not require any splicing or otherwise combining of DNA encoding different portions of the antibody chain.

Claim 31 of the application was rejected under 35 U.S.C. § 102(b) as anticipated by Harris et al., EP 314,161. This

reference was cited as teaching method for making therapeutic compositions comprising a mixture of a recombinant human antibody and a physiologically acceptable diluent. This rejection has been obviated by the cancellation of claim 31.

Claims 3, 6 and 17-24 have been rejected under 35 U.S.C. § 103 as obvious over Gillies et al. in view of Foung et al. and Ehrlich et al. The examiner asserted that these claims are directed to methods for the production of recombinant chimpanzee or old world monkey antibodies specific for hepatitis virions. Gillies et al. were cited for teaching methods of producing recombinant human antibodies from cDNA libraries. Foung et al. were cited as teaching the production of chimpanzee monoclonal antibodies specific for non-A, non-B hepatitis virus and that desirable alternative sources of B-cells were non-human primates because antibodies from phylogenetically related primates would not be expected to engender an immune response upon administration to humans and the primates could be immunized with antigens that cannot be administered to humans for ethical reasons. Ehrlich et al. were cited as indicating that human antibodies are non-immunogenic in Rhesus monkeys and that chimpanzee immunoglobulin genes have highly similar nucleic acid sequences. The examiner asserted that by coupling these techniques, one skilled in the art would have expected that the use of monkey or chimpanzee antibodies in humans would not lead to significant immunological responses in humans. The nucleic acids encoding these antibodies could have been isolated from

primate B-cells using the teachings of Gillies et al. in view of the high degree of sequence homology between primate immunoglobulin genes and those of human origin. The examiner concluded that the combined teachings of the references would allow for the isolation of primate nucleic acid which encodes immunoglobulin molecules potentially useful for therapy or diagnostic purposes and that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. This rejection as applied to claims 3 and 6 is traversed. The other claims included in this rejection have been canceled.

Both of claims 3 and 6 of this application are dependent upon claim 1. As discussed above, claim 1 provides a method for producing a recombinant antibody which includes inserting the cDNA encoding both the variable and constant regions of each of the light and heavy chains of the antibody of interest into an expression vector, transfecting a host cell with the expression vector and then culturing the transfected host cell under conditions conducive to the production of the light and heavy chains of the antibody and then isolating the antibody produced. Also as discussed above, the Gillies et al. reference teaches away from the method of the claim because Gillies et al. teach that the DNA encoding the constant region of each chain should be obtained by using a combination of cDNA and genomic DNA. The two secondary references cited by the examiner do not overcome the deficiencies of the Gillies et al. reference. Neither Foung et

al. nor Ehrlich et al. teach or suggest any method for the production of recombinant antibodies, much less that a recombinant antibody can be produced by obtaining the cDNA encoding the entire constant and variable regions of each of the heavy and light chains of the antibody, inserting the cDNA into an expression vector under the control of expression signals, transfecting a cell with the expression vector and then culturing the cell under antibody-producing conditions.

Claim 11 was rejected under 35 U.S.C. § 103 as being obvious over Gillies et al. in view of Larrick et al. This claim is directed to a method of producing recombinant antibodies using micro-preps of RNA. The examiner stated that Gillies et al. teach methods for the production of recombinant human antibodies from cDNA libraries. Larrick et al. was cited as teaching that the variable regions of an antibody produced by a single B cell can be isolated. The examiner asserted that the combined techniques taught in the two references would allow for the isolation of an immunoglobulin gene from B cells and its subsequent recombinant expression. This rejection is traversed.

The method of claim 11 is not obvious in view of the cited references. The shortcomings of the Gillies et al. reference have been discussed above and are equally applicable here. The Larrick et al. reference does not compensate for those shortcomings. One of skill in the art who was familiar with the teachings of these two references would not be led to construct an expression vector in which the DNA encoding the constant and

variable regions of each chain of the antibody of interest are provided by cDNA. Gillies et al. teach that it is necessary to use genomic DNA as the source for part of the DNA encoding the constant region of the antibody chain. The Larrick et al. reference does not address this issue. This reference teaches a method of amplifying human monoclonal antibody variable region genes using PCR. Using this method, it would not be possible to amplify the DNA encoding both the variable and constant regions of an antibody heavy or light chain. A constant region downstream promoter is used to amplify the variable region of the gene, taking advantage of the conservation of the sequence in this region. No downstream promoters are taught which would enable the amplification and cloning of the entire gene including both the constant and variable regions. The combined teachings of these references do not teach or suggest the method set forth in claim 11 of this application.

Claim 25 of the application was rejected under 35 U.S.C. § 103 as obvious over Gillies et al. in view of Foung et al., Ehrlich et al. and Harris et al. This rejection has been obviated by the cancellation of claim 25.

Applicants respectfully submit that, in view of the

foregoing amendments and discussion, the claims of this application are in condition for allowance.

Respectfully submitted,

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